Office of Clinical Pharmacology Review

NDA Number	215422
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Submission Date	1/22/2021
Submission Type	Original NDA (505(b)(2))
Product Name	Lyvispah® (baclofen granules)
Dosage Form and Strength	Granules, 5 mg, 10 mg and 20 mg
Route of Administration	Oral
Proposed Indication	Treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity
Applicant	Saol Therapeutics Research Limited
Associated IND	140719
OCP Primary Reviewer	Yifei Zhang, Ph.D.,
OCP Team Leader	Bilal AbuAsal, Ph.D.

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1. Executive Summary

Saol Therapeutics Research Limited submitted an original New Drug Application (NDA) to support the approval of Baclofen Granules (Lyvispah®) for the treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. The submission is via the 505(b)(2) pathway using Baclofen Tablets A072235 (held by Teva) as the Reference Standard (RS).

Baclofen Granules are provided in a free-flowing granular form in stick pack configurations at strengths of 5 mg, 10 mg, and 20 mg. The proposed dosing regimen of Baclofen Granules is the same as Baclofen Tablets: 5 mg TID for three days, 10 mg TID for three days, 15 mg TID for three days, and 20 mg TID for three days. Additional increases may be necessary up to the maximum recommended dosage of 80 mg daily (20 mg four times a day).

The approval was supported by results from two pharmacokinetic studies conducted in healthy subjects to demonstrate the bioequivalence between Lyvispah and the RS. Study Saol 1001-01 is the pivotal Phase 1 bridging study that demonstrated bioequivalence of baclofen granules (20 mg) and the RS (20 mg). This study also evaluated the pharmacokinetics of Lyvispah when administered with or without water, or in soft food. When Lyvispah was taken with or without water or soft food, the baclofen exposure metrics (AUC and C_{max}) were all within the bioequivalence criteria compared with the exposure of the RS after administration with water under fasted conditions.

Study Saol 1001-02 demonstrated dose-proportionality of the granule formulation across the dose range of 5 mg, 10 mg, and 20 mg. This study also evaluated the effect of high-fat meal on the PK of baclofen granules. Administration of high fat meal led to decrease in AUC by 10% and C_{max} by 29%, which is comparable to the effect of high fat meal on RS based on data from ANDA 074584. The PK studies conducted by the applicant provided an adequate scientific bridge for this application to rely on the labeling information of RS.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability study Saol 1001-01. OSIS determined that the inspections were previously conducted for other applications within the surveillance interval, and therefore not warranted at this time.

The applicant is proposing to advance the registration for Lyvispah for use in pediatrics (ages 12 and above) and adults, consistent with the current authorizations for RS.

The focus of this review is to confirm the adequacy of the PK bridge between Lyvispah and the RS and evaluate the dosing instruction with regard to food.

2. Recomendation

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA and recommends approval based on the bioequivalence demonstrated between Baclofen Tablet 20 mg to that of the baclofen granules 20 mg following a single dose in healthy subjects, and the dose-proportionality of the PK across the dose range of 5 mg, 10 mg, and 20 mg granules.

The baclofen granules (Lyvispah) can be taken with or without water or soft food, since it was demonstrated that the granule formulation was equally bioequivalent to Baclofen Tablets, whether administered with or without water, or in soft foods such as applesauce.

Study results showed 29% decrease in C_{max} and a 10% decrease in AUC of baclofen when administered with a standard high fat meal. This information will be included in section 12.3 of the labeling. However, no specific recommendation will be provided on administering with regard to food except for water and soft food, to be consistent with the approved label of RS.

3. Background and Regulatory History

Lyvispah is designed to rapidly dissolve in the mouth after oral administration, and the rationale is to provide an alternative oral dosage form for ease of administration especially for those patients with difficulty swallowing tablets. The applicant is proposing to advance the registration for Lyvispah with labeling for use in pediatrics (ages 12 and above) and adults, consistent with the current authorizations for Baclofen Tablets.

The applicant conducted two pharmacokinetic studies to demonstrate the bioequivalence of the new formulation of baclofen granules to that of the RS (**Table 1**), as a means of establishing a bridge to the demonstrated safety and efficacy performance of the tablet dosage form.

Table 1 Summary of Clinical Studies

Study ID	Objective	Study Design	Test Product(s); Dose; Dosage Regimen (oral)
Saol 1001-01 (Prot No. 190104)	Single dose fasted; test vs reference Baclofen Tablet	Open label, randomized 5-way crossover study with 7-day washout period. Healthy subjects (n=28)	A: Baclofen Tablets 20mg (Reference) with water B: Baclofen Granules 20mg, without water C: Baclofen Granules 20mg, with water D: Baclofen Granules 20mg, in soft food E: Baclofen Granules (4 x 5mg)
Saol 1001-02 (Prot No. 190342)	Single dose fasted vs fed; proportionality across dose range	Open label, randomized 4-way crossover study with 7-day washout period. Healthy subjects (n=29)	A: Baclofen Granules 20mg, with water, fasted B: Baclofen Granules 20mg, with water, fed C: Baclofen Granules 5mg, with water, fasted D: Baclofen Granules 10mg, with water, fasted

Study Saol 1001-01 is a pivotal Phase 1 bridging study that demonstrated bioequivalence of baclofen granules (20 mg) to the RS (20 mg). This study also evaluated the bioequivalence of the two formulations when baclofen granules were administered with or without water, or in soft food. Study Saol 1001-02 demonstrated the dose-proportionality of the granule formulation across the dose range of 5 mg, 10 mg, and 20 mg. This study also evaluated the effect of high-fat meal on the PK of baclofen granules.

4. Summary of Pivotal Relative BA/BE and Food Effect Study

The sponsor conducted two pharmacokinetic studies to demonstrate the bioequivalence of baclofen granules to the RS, and to further characterize the dose proportionality and food effect for baclofen granules.

Study Saol 1001-01

Title: A Single-Dose Fasted Comparative Bioavailability Study of Baclofen Granules and Baclofen Oral Tablets

Primary Objectives

To assess the systemic absorption and PK of a single 20 mg dose of baclofen granules when administered with water, without water or in soft foods, as compared to an established oral dose of baclofen tablets 20 mg in fasted state.

Methodology

This was an open-label, randomized, five-way crossover, single-dose study comparing the PK of baclofen administered as an oral granule 20 mg presentation (whether with or without water or in soft foods) relative to that of a 20 mg oral baclofen tablet reference dose under fasting conditions. Test and reference products are summarized in **Table 2** below.

Table 2 Treatment Description of Study Saol 1001-01

Treatment	Description
Treatment A	Baclofen tablets 20 mg
Treatment B	Baclofen granules 20 mg, without water
Treatment C	Baclofen granules 20 mg, with water
Treatment D	Baclofen granules 20 mg, in soft food
Treatment E	Baclofen granules 20 mg, with water, provided as 4 sachets of 5 mg each

Subjects who met the eligibility criteria were randomized to receive a single dose (20 mg) of baclofen in a crossover approach in accordance with the randomization scheme to receive each of Treatments A, B, C, D, and E in Periods 1 to 5 of the study. Subjects were fasted for at least

10 hours prior to the first study drug treatment. The treatment phases were separated by a washout period of 7 days.

PK Sampling

Blood samples were collected at pre-dose, 15, 30, and 45 minutes and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 48 hours post-dose in each period.

Criteria for PK Comparison

The following PK parameters were calculated for baclofen using standard non-compartmental methods: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, λz, and $t_{½}$. Comparisons of baclofen exposures including AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were made for the following pairs of treatment groups: B/A, C/A, D/A, and E/C. The difference is considered not significant if the 90% confidence intervals (CI) for the ratios of geometric means based on LSM from the ANOVA of the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} are within 80% to 125%.

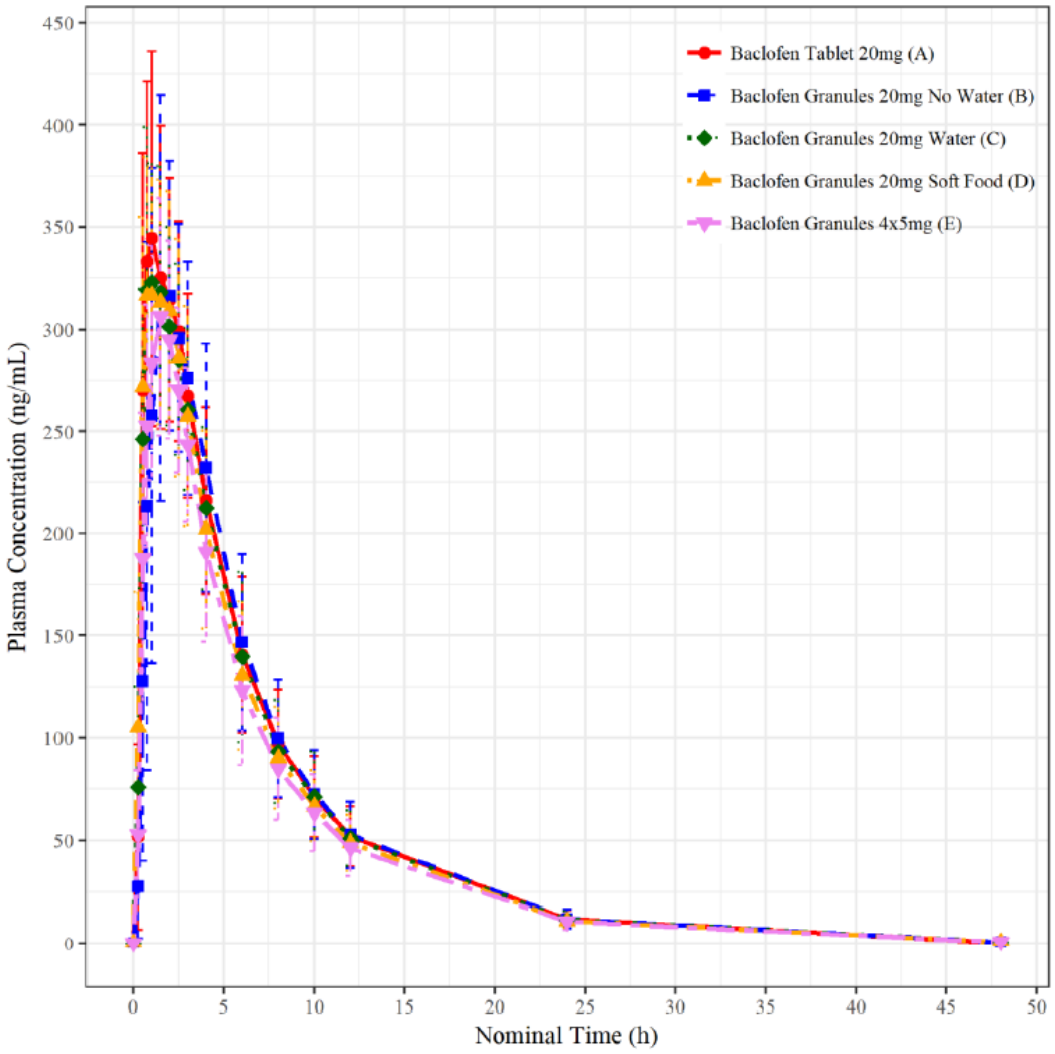
Results

The plot for the mean (±SD) baclofen plasma concentrations for each treatment over the sampling period are presented in **Figure 1**. The descriptive statistics for PK parameters of each treatment are shown in **Table 3**. **Table 4** summarized the ratio of PK parameters and CI.

Based on the results, it can be concluded that Treatment B (baclofen granules 20mg without water), C (baclofen granules 20 mg, with water), and D (baclofen granules 20 mg, in soft food) showed a comparable baclofen exposure, in terms of rate and extent of systemic absorption, to Treatment A (the RS baclofen tablets 20 mg administered with water). These results demonstrated that the baclofen granules formulation is bioequivalent to baclofen tablets. and the bioequivalence with the tablets was not affected regardless of whether the baclofen granules were administered with or without water or soft food.

The treatment E (baclofen granules 20 mg, with water, provided as 4 sachets of 5 mg each) was compared with treatment C (baclofen granules 20 mg, with water). Results showed that the 90% CI of GLSM ratios for AUC and C_{max} were both within the bioequivalence limit (80%-125%). (**Table 4**), which could support the dose proportionality. However, the sponsor conducted additional dose proportionality assessment in Study Saol 1001-02.

Figure 1: Mean (±SD) Baclofen Plasma Concentration



Source: Clinical study report (Saol 1001-01) Figure 11.4.2.3-1, Page 56

Table 3 Summary of Pharmacokinetic Parameters for baclofen by treatment

Treatment/Number of subjects	AUC_{0-t} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	t_{max} (h)
A (N = 29)	2350.3 ± 484.9	2409.4 ± 479.5	378.8 ± 74.0	5.4 ± 0.8	1.0 (0.5, 3.0)
B (N = 29)	2348.7 ± 499.9	2398.0 ± 488.9	359.1 ± 67.7	5.5 ± 0.8	1.5 (0.7, 4.0)
C (N = 28)	2325.4 ± 425.9	2372.7 ± 417.3	353.9 ± 72.4	5.7 ± 0.9	1.5 (0.5, 3.0)
D (N = 29)	2263.4 ± 446.3	2306.0 ± 437.4	358.2 ± 59.9	5.9 ± 1.1	1.5 (0.5, 4.0)
E (N = 29)	2090.9 ± 419.8	2134.9 ± 416.6	318.4 ± 48.3	5.9 ± 1.0	1.5 (0.7, 3.0)

Source: Clinical study report (Saol 1001-01) Table 11.4.2.3-1, Page 57-59. Note: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} is presented as geometric mean ± SD, $t_{1/2}$ as mean ± SD, and t_{max} as median (min, max)

Table 4 Ratio of PK Parameters and Confidence Intervals

	GLSM Ratio % (90% CI Lower and Upper Bound %)		
	AUC_{0-t} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	C_{max} (ng/mL)
B/A	99.8 (97.0, 102.7)	99.4 (96.7, 102.2)	94.6 (88.2, 101.4)
C/A	99.9 (96.6, 103.2)	99.3 (95.9, 102.9)	94.1 (88.4, 100.2)
D/A	96.6 (93.9, 99.4)	96.0 (93.4, 98.7)	94.7 (90.1, 99.5)
E/C	90.2 (86.5, 94.0)	90.3 (86.7, 94.0)	90.4 (85.8, 95.1)

Source: Clinical study report (Saol 1001-01) Table 11.4.2.3, Page 61-69

Study Saol 1001-02

Title: A Single-Dose Comparative Bioavailability Study of Baclofen Granules

Primary Objectives: To assess the systemic absorption and PK of a single 20 mg dose of baclofen granules when administered with water in the fasted state as compared with the same dose administration taken in the fed state; and to assess the dose-proportionality of the PK across the dose range of 5 mg, 10 mg, and 20 mg with water in a fasted state.

Methodology: This was a randomized four-way single-dose crossover study to compare the PK of baclofen administered as a 20 mg oral dose of granule formulation under fed (standard high fat meal) versus fasted conditions. Dose-proportionality of the PK was assessed across the dose range of 5 mg, 10 mg, and 20 mg granules. The treatments were listed in **Table 5**, separated by a washout period of at least seven days between each phase.

Table 5 Treatment Description of Study Saol 1001-02

Treatment	Description
Treatment A	Baclofen granules 20 mg, with water, fasted
Treatment B	Baclofen granules 20 mg, with water, fed
Treatment C	Baclofen granules 5 mg, with water, fasted
Treatment D	Baclofen granules 10 mg, with water, fasted

PK Sampling: Blood samples were collected prior to drug administration and at 15, 30, and 45 minutes and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 48 hours post-dose in each period.

PK Assessment: The following PK parameters were calculated by standard non-compartmental methods for baclofen: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, λ_z, $t_{½}$.

Assessment of Food Effect

For the assessment of food effect on baclofen, analysis of variance (ANOVA) was performed on untransformed t_{max}, λ_z, and $t_{½}$ and ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} at the alpha level of 0.05. The ratio of geometric means (B/A) and 90% confidence interval (CI) for the ratio of

geometric means, based on least-squares means (LSM) from the ANOVA of the ln-transformed data, were calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. No food effect was to be concluded if the 90% confidence intervals for the ratio of geometric means (B/A), based on LSM from the ANOVA of the ln-transformed baclofen AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, was within 80% to 125%.

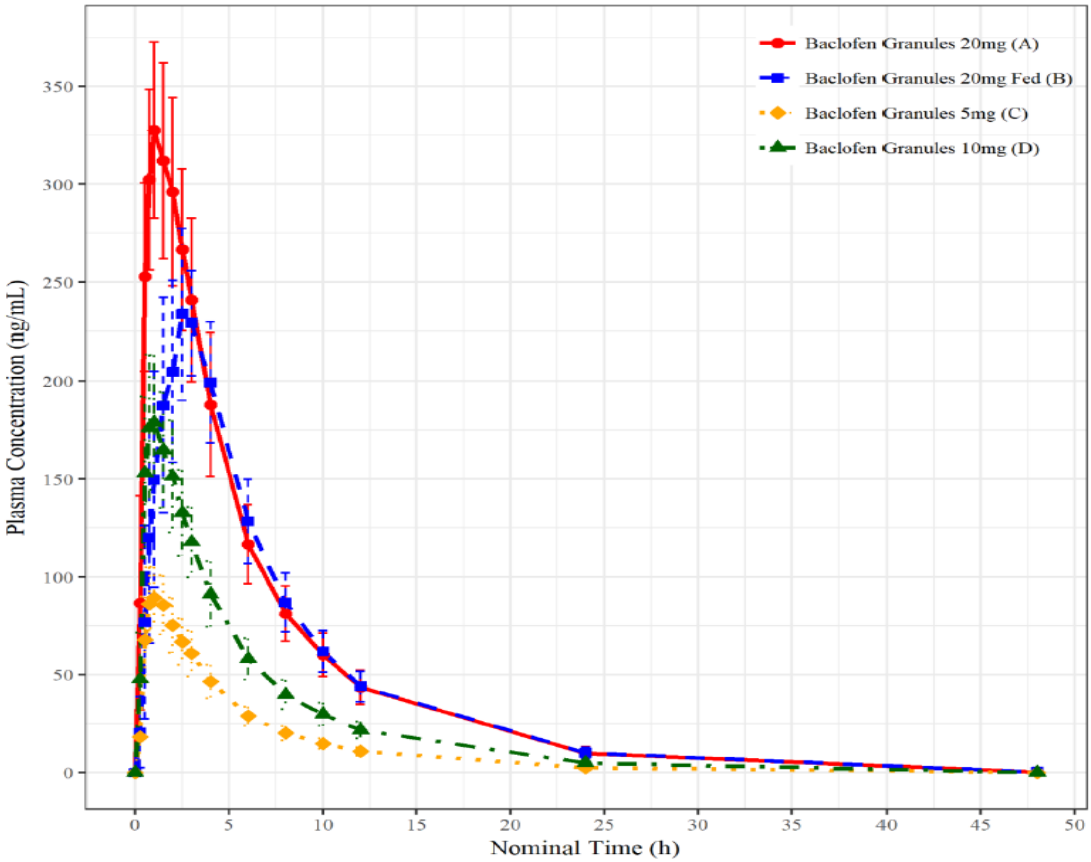
Assessment of dose proportionality

With the data from treatments at fasted state, dose-proportionality was assessed for each of the parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, using the power model. For baclofen $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}, the 90% confidence intervals of slope were compared to the lower and upper bounds determined by dose range ratio.

Results

The plot for the mean (±SD) baclofen plasma concentrations over the sampling period are presented for in **Figure 2** below.

Figure 2 Mean (±SD) Baclofen Plasma Concentration



Data Source: Clinical study report (Saol 1001-02) Figure 11.4.2.3-1, Page 52

The geometric mean ratios for exposures at fed vs. fasted state with 90% CI are shown in **Table 6** below. High-fat meal led to approximately 10% decrease in AUC_{0-t} and $AUC_{0-\infty}$, and 29% decrease in C_{max}, following a single oral dose of 20 mg of baclofen granules with water. Dose proportionality of the PK was supported across the dose range of 5 mg, 10 mg, and 20 mg with water in a fasted state (**Table 7**).

Table 6 Ratios of Treatment B (Baclofen granules 20 mg, with water, fed) vs. Treatment A (Baclofen granules 20 mg, with water, fasted), 90% Geometric Confidence Intervals, Intra-Subjects CV (%) and p-values for Baclofen

		Geometric LSM			90% Geometric C.I.			p-values
Comparisons	Parameter (Unit)	Treatment B	Treatment A	Ratio (%)	Lower (%)	Upper (%)	Intra-Subject CV (%)	Treatment
B vs. A	AUC_{0-t} (h*ng/mL)	1832.35	2039.94	89.82	86.81	92.94	7.07	<0.0001
B vs. A	AUC_{0-inf} (h*ng/mL)	1886.28	2106.38	89.55	86.39	92.83	7.45	<0.0001
B vs. A	C_{max} (ng/mL)	241.26	338.28	71.32	67.05	75.86	12.82	<0.0001

Source: Clinical study report (Saol 1001-02) Table 11.4.2.3-3, Page 60

Table 7 Analysis of Dose Proportionality for Baclofen

			Power Model Analysis			
Dose Levels Included	PK Parameter (unit)	Number of Subjects Included in the Analysis	Slope Estimate	90% CI for Slope	Interval Criterion	Criterion Satisfied[1]
5 mg, 10 mg, 20 mg	AUC_{0-t} (h*ng/mL)	27	0.9936	(0.9745, 1.0127)	(0.8390, 1.1610)	Yes
	AUC_{0-inf} (h*ng/mL)	27	0.9899	(0.9714, 1.0084)	(0.8390, 1.1610)	Yes
	C_{max} (ng/mL)	27	0.9204	(0.8835, 0.9573)	(0.8390, 1.1610)	Yes

Source: Clinical study report (Saol 1001-02) Table 11.4.2.3-5, Page 63. Note [1]: If the reported 90% confidence interval is entirely contained within the interval criterion of (0.8390, 1.1610), then dose proportionality is supported across the investigated dose range, for the particular dosing regimen.

The results showed that the high fat meal did not significantly affect the AUC (approximately 10% decrease in AUC_{0-t} and $AUC_{0-\infty}$). However, the C_{max} was decreased by ~29% (CI: 67.05, 75.86) which was out of the 90% CI specified in bioequivalance criteria.

Based on reviewer's cross-study comparison between fed and fasted state for the RS at 20 mg dose from ANDA 074584, administration with standardized high-fat, high-calorie breakfast led to 29% decrease in C_{max} and 18% decrease in $AUC_{0-\infty}$. The effect of high fat meal on the reference product from the ANDA appears to be comparable with that on baclofen granules in the current submission.

The USPI for the RS did not include any statement about the dosing instruction with regard to food or the effect of food on baclofen absorption. Without additional evidence to evaluate the clinical significance of the difference in C_{max}, the labeling of baclofen tablets should reflect the labeling of RS, without specific recommendation on administering the drug with regard to food except for water and soft food.

5. Bioanalytical Method Validation

A validated liquid chromatographic method was used for determining the baclofen concentrations in human plasma. The samples were prepared by an automated protein precipitation procedure and analyzed by liquid chromatography with tandem mass spectrometry detection (LC/MS/MS). The methods met the acceptance criteria for bioanalytical methods according to the FDA Bioanalytical Method Validation Guidance for Industry. Performance characteristics and validation attributes of the bioanalytical method are summarized in **Table 8**.

Table 8 Summary of Bioanalytical Method and Validation Characteristics

Parameter	**Parent Drug**
Analyte	Baclofen
Internal Standard (IS)	Baclofen-d_5
Lower Limit of Quantitation (LLOQ)	1.00 ng/mL
Mean recovery of analyte (%)	91.54, 93.83 and 96.38% at low, medium, and high QC levels (3 ng/mL, 500 ng/mL, and 750 ng/mL)
Mean recovery of IS (%)	94.08%
Standard curve concentrations (ng/mL) and linearity (r^2)	1.00, 2.00, 20.00, 100.00, 200.00, 400.00, 800.00 and 1000.00 ng/mL; Linearity: $r^2 \geq 0.9960$
Between-run accuracy and precision	Biases: -2.53 to 1.11%; CV: 1.68 to 5.58%
Within-run accuracy and precision	Biases: -4.06 to 3.83%; CV: 1.02 to 8.24%
Bench-top stability (hrs) (equivalent to short-term stability of analytes in matrix)	24h 25min at room temperature 24h 04min at 4°C
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	95 days at -20°C and at -80°C

Processed stability (hrs) (equivalent to post-preparative stability)	144h 24min at room temperature
Freeze-thaw stability in matrix	4 cycles at -20°C and -80°C
Stock stability (days) (equivalent to long-term stability of analyte or IS in solution)	77 days at -20°C
Matrix selectivity	No significant interference in 8 tested matrices for baclofen and IS; No effect on the quantitation of analytes

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/s/

YIFEI N ZHANG
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BILAL S ABU ASAL
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